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TETRAHYDROISOQUINOLINE-AND TETRAHYDROBENZAZEPINE DERIVATIVES AS IGF-1R INHIBITORS

znd Continuing Data

9/8/10 This application is a 371 of PCT/CH04/00147 filed March 12, 2004.

FIELD OF THE INVENTION

The present invention relates to novel compounds capable of down-regulating or inhibiting the expression or function of the insulin-like growth factor-1 receptor (IGF-1R). The invention is also directed to methods of down-regulating or inhibiting IGF-1R expression or function in order to prevent and/or treat cancer and other abnormal cell growth, and metabolic as well as blood vessel proliferate disorders, in which uncontrolled expression of this receptor is observed.

BACKGROUND OF THE INVENTION

The insulin-like growth factor receptor (IGF-1R) is one of 58 trans-membrane tyrosine kinase receptors present in humans [Review: Structure and function of the Type 1 insulin-like growth factor receptor. T.E.Adams et al. Cell. Mol. Life Sci. 57 (2000) 1050-1093]. Genetic evidence and studies on cells lacking the IGF-1 receptor have demonstrated that it is required for optimal growth, but not an absolute condition for growth [Baserga et al. Biochim. Biophys. Acta 1332(1997) 105-126]. An expression of the IGF-1 receptor protects cells from apoptosis and seems to be a requirement for the establishment and maintenance of the transformed phenotype both in vitro and in vivo [R. Baserga et al. Biochim. Biophys. Acta 1332 (1997) 105-126]. Several *in vitro* and *in vivo* studies have demonstrated that inhibition of the expression or function of the IGF-1 receptor reverses the transformed phenotype and inhibits tumor cell growth. The techniques used in these studies include neutralizing antibodies [Kalebic et al. Can-